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MINI REVIEW

Bexarotene: a promising anticancer agent

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Abstract Retinoids are biologically active derivatives of vitamin A, which play essential roles in embryonic or adult cell behavior modulating cell proliferation, differentiation and apoptosis. The biologic effects of retinoids are mediated by two distinct families of intracellular receptors: retinoid acid receptors (RARs)-α, -β and -γ and retinoid X receptors (RXR)-α, -β and -γ. Bexarotene is a selective RXR agonist, which exerts its effects in blocking cell cycle progression, inducing apoptosis and differentiation, preventing multidrug resistance, and inhibiting angiogenesis and metastasis, making it a promising chemopreventive agent against cancer.

Keywords Bexarotene · Cell cycle · Apoptosis · Differentiation · Multidrug resistance

Introdution

Retinoids, natural and synthetic derivatives of vitamin A, belong to the steroid hormone family of molecules, and are physiologic regulators of a large number of essential biologic processes including embryonic development, vision, reproduction, bone formation, metabolism, organogenesis, organ hematopoiesis, differentiation, proliferation, and apoptosis [1]. These compounds bind to and active one or more nuclear retinoids receptors to modulate gene expression. It is known that the biologic effects of retinoids are mediated by two distinct families of intracellular receptors: retinoid acid receptors (RARs)-α, -β and -γ and retinoid X receptors (RXR)-α, -β and -γ, which are ligand-activated transcription factors and members of the steroid hormone receptor superfamily [2]. RARs can homodimerize or heterodimerize with RXRs to affect differentiation and cell growth, while RXRs can form heterodimers with other nuclear hormone receptors [vitamin D receptor, thyroid hormone receptor and peroxisome proliferator activated receptors (PPAR)], the heterodimer binds DNA and affects the function of genes downstream of retinoid acid response elements (RAREs). It may also play a role as a transcriptional repressor or compete with transcription factors for coactivator molecules [3, 4].

Bexarotene is a novel oral synthetic rexinoid that specifically binds to RXRs and does not have significant RAR binding and transactivation of RAR-responsive genes, except at higher dose levels [5]. Activation of RXR and its heterodimer partners lead to multitargeted approach which suggests bexarotene may be a particularly active agent in the treatment of malignancies. In addition, preclinical, clinical, and epidemiologic data suggest that retinoids may play a role in cancer prevention [6, 7] and treatment [8]. Bexarotene has been approved for the treatment of cutaneous T-cell lymphoma (CTCL) in patients whose disease is refractory to at least one prior systemic therapy [9]. In addition, in solid tumors, bexarotene has shown particular promise in the treatment of non-small cell lung cancer (NSCLC) [10]. There is a large body of literatures on clinical and preclinical studies using bexarotene for the treatment of cancer as summarized in Table 1. In this review, we describe that bexarotene possesses antiproliferative and proapoptotic properties, making it a promising chemopreventive agent against cancer.

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Table 1 Bexarotene in clinical trails or approved for therapy

Chemical (trade name/company)	Indications/status	Treatment regimens	Response rates	Side effects	Combination therapies
Bexarotene (Targretin/Ligand Pharmaceuticals)	Launched: NSCLC, CTCL [11]	CTCL: 300 mg/m^2/day [11, 27, 28] NSCLC: 400 mg/m^2/d [12]	CTCL: 30% [11] NSCLC: Overall tumor response rate: 16.7%. Disease stabilization: 37% [12]	Hyperlipidemia Headache Skin toxicity Hypothyroidism Asthenia Leukopenia Nausea [11, 12, 16, 21, 29–36]	Prevents and reverses drugs resistance in NSCLC and prostate cancer [13, 37] Potentiates the toxicity of drugs and increases rate of apoptosis [13, 27, 29, 38] Synergies the effects of narrowband ultraviolet B phototherapy in patients with mycosis fungoides [30, 39] In combination with theophylline/rolipram/3-isobutyl-1-methylxanthine induced apoptosis via tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and DR5 death receptor pathway in acute myeloid leukemias (AML) [40] In combination with cisplatin/vinorelbine) did not increase survival in patients with advanced NSCLC [31] In combination with interferon alfa-2b not increase the response rate in patients with cutaneous T cell lymphoma [41]
	Phase III: breast cancer [12–15]				
	Phase II: mycosis fungoides and Sézary syndrome, metastatic melanoma, parapsoriasis, psoriasis [16–19]				
	Phase I: non-M3 acute myeloid leukemia, refractory cancers, aerodigestive tract cancer, chronic severe hand dermatitis [20–23]				
	Phase I/II: alopecia areata [24]				
	Clinical trial: differentiated thyroid carcinoma, lymphomatoid papulosis [25, 26]				

Inhibition of cell cycle progression

Transitions between the various phases of the cell cycle are controlled by many cyclins, cyclin-dependent kinases (CDKs), and cell cycle inhibitors. Treatment of lung cancer cells with bexarotene was link to triggering of G1 and/or G2/M arrest by the modulation of critical checkpoint proteins [42], concomitant a loss of viability and more pronounced inhibition of clonogenic proliferation, and downregulation the expression of cyclin D1 resulting in inhibition of cell growth [43]. Bexarotene can activate p53 by phosphorylation at Ser15, which influences the binding of p53 to promoters for cell cycle arrest, induces p73 upregulation, and, in concordance, also modulates some p53/p73 downstream target genes, such as p21, Bax, survivin and cdc2 [44]. Bexarotene represses the expression of cyclin D1, cyclin D3, total epidermal growth factor receptor (EGFR), and phospho-EGFR expression with dosage-dependent in non-small cell lung cancer [45]. In addition, bexarotene can inhibit the formation of both estrogen receptor-negative and estrogen receptor-positive breast cancer in preclinical models and controls the expression of growth-regulatory biomarkers, such as insulin-like growth factor-binding protein 6 (IGFBP-6), RAR-β, or cyclin D1 [46].

Induction of apoptosis

Apoptosis is a multistep process and a great number of genes have involved in the control or execution of apoptosis. Caspases play a crucial role in apoptosis. The apoptotic caspases are separated into a hierarchy of initiators (caspase-2, -8, -9 and -10) and executioners (caspase-3, -6, and -7) [47]. In apoptosis, there were at least two classical pathways that lead to activation of effecter caspases such as caspase-3. The first pathway involves activation of the death receptor tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) [48], leading to activation of caspase-8. The other pathway is initiated by mitochondrial injury, finally causing activation of caspase-9. Once activated, initiator caspases can activate effector caspases, eventually cleaving poly-(ADP-ribose) polymerase (PARP) and producing apoptosis. The cleavage of PARP is used as a hallmark of apoptosis by various antitumor agents. Survivin is a member of the inhibitor of apoptosis protein (IAP) family which suppresses caspase activity and protects cells from apoptosis induced by a variety of agents [49]. Zhang et al. [50] reported that bexarotene treatment caused apoptosis of CTCL cell lines in association with activation of caspase-3 and cleavage of PARP, as well as down-regulation of survivin. In KG1a cells [apoptosis-resistant acute myeloid leukemia cell line

(AML)], bexarotene activated caspase-8; in unmodified ML-1 cells (apoptosis-sensitive AML cell line) bexarotene enhanced programmed cell death via truncation of Bid and release of cytochrome C [50]. In mouse lung tumors, Alyaqoub et al. [51] demonstrated that bexarotene decreased the mRNA expression of Caspase-3, Dnmt-3a, EP3, and survivin, as well as the expression of the Cyclin E1, estrogen receptor-alpha, and iNOS genes.

Induction of differentiation

The natural progression of a cell in vivo is to divide, differentiate into a functional cell and then eventually undergo cell death. In the cancerous state a cell's natural progression is interrupted and unregulated cell division progresses. Therefore, the inhibition of cell growth and the induction of differentiation in malignancies could be the key to a cure. Bexarotene exerts its effect on growth inhibition and differentiation induction in colon cancer cells in vitro and in vivo, and the ability of an RXR and PPARγ agonist combination to synergistically enhance the induction of differentiation in colorectal cancer [52]. In vitro, bexarotene has long been known to inhibit clonal growth and induce differentiation of the HL-60 leukemic cell line as well as leukemic cells from patients with AML [53]. Recent reports have suggested that bexarotene may have enhanced differentiation effects in primary AML cells when subordination by RAR protein is released with a cAMP agonist [40]. Further studies are required to investigate the molecular mechanisms by which bexarotene inhibit cell growth and induce differentiation.

Prevention of multidrug resistance

Intrinsic or acquired resistance to chemotherapeutic drugs is the major obstacle for the successful chemotherapy. The most frequent form of resistance observed in cancer patients is multidrug resistance (MDR). It has been established that membrane proteins, notably multidrug resistance (MDR), multidrug resistance protein (MRP), and breast cancer resistance protein (BCRP) of the ATP binding cassette (ABC) transporter family encoding efflux pumps, play important roles in the development of multidrug resistance [54]. MRP1 and p-glycoproteinare (P-gp) frequently overexpressed in drug-resistant cancer cells; the latter is encoded by the human MDR1 gene [55]. Bexarotene has been shown to be an efficacious chemopreventive and chemotherapeutic agent in preclinical breast cancer, prostate cancer and non-small cell lung cancer models [37, 56, 57]. Yen et al. [58] have shown that bexarotene can prevent the development of paclitaxel resistance in the human NSCLC Calu3 cells. Bexarotene in combination with paclitaxel produced a synergistic growth inhibition in a rat carcinogen-induced mammary tumor cell line in vitro and resulted in a significant increase in overall objective response compared to single agents alone in vivo [59]. The molecular mechanism of bexarotene in modulating MDR1 gene expression may relate to the inhibition of nuclear factor (NF)-kappaB activity. Inhibition of NF-kappaB activity in NSCLC cell lines increased the sensitivity to chemotherapy-induced apoptosis [60]. NF-kappaB also controls the expression of the mdr1 gene. In human colon cancer cells, inhibition of NF-kappaB reduced MDR1 mRNA and Pgp expression [61]. PI3K/Akt pathway is involved in MDR in lymphoma cell lines and PI3K/Akt inhibition correlates down-regulation of NF-kappaB activity and inhibition P-gp function [62]. Bexarotene may directly or indirectly antagonize steroid and xenobiotic receptor to prevent MDR1 expression [58].

Inhibition of angiogenesis and metastasis

Metastasis, the spread of cells from a primary neoplasm to distant sites where they grow, contributes to the death of most cancer patients. It has been well established that tumor metastasis is a complex multistep process that requires migration, invasion and angiogenesis. Angiogenesis plays an important role in tumor metastasis and progression and thus inhibiting angiogenesis is a promising strategy for treatment of cancer [63]. Matrix metalloproteases are key enzymes involved in migration and local invasion of tumor cells. A number of angiogenic stimulators including vascular endothelial growth factors (VEGF), basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), platelet-derived endothelial cell growth factor (PDGF) were identified to stimulate endothelial cell proliferation resulting in angiogenesis [64]. Yen et al. [65] have shown that bexarotene decrease migration and invasiveness of tumor cells in a dose-dependent manner. In A549 cells, treatment with bexarotene resulted in reduction in matrix metalloproteinases (MMPs), VEGF, EGF and increase in tissue inhibitors of matrix metalloproteinases (TIMPs) secretion. Furthermore, bexarotene inhibited angiogenesis by directly inhibiting human umbilical vein endothelial cell growth and indirectly inhibiting tumor cell-mediated migration of human umbilical vein endothelial cells through Matrigel matrix. Analysis of tumor-conditioned medium indicated that bexarotene decreased the secretion of angiogenic factors and matrix metalloproteinases and increased the tissue inhibitor of matrix metalloproteinases. The inhibitory effect of bexarotene on angiogenesis and metastasis was through activation of its heterodimerisation partner PPARγ [65].

Conclusion

Retinoids are biologically active derivatives of vitamin A that play essential roles in regulators of differentiation, proliferation, apoptosis. The biologic effects of retinoids are mediated by two distinct families of intracellular receptors: RAR-α, -β and -γ and RXR-α, -β and -γ. Bexarotene is a selective RXR agonist which has been approved by the Food and Drug Administration for CTCL and NSCLC. Herein, we describe that bexarotene inhibits cell cycle progression with G1 and/or G2/M arrest and downregulation of cyclin D; induces apoptosis and differentiation with activation of caspase-3 and cleavage of PARP, as well as down-regulation of survivin; prevents and overcomes multidrug resistance with modulating MDR1 expression; inhibits angiogenesis and metastasis with reduction in MMPs, VEGF, EGF and increase in TIMPs secretion, making it a promising chemopreventive agent against cancer.

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